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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/809,920	03/16/2001	Taka-Aki Sato	0575/51902-A-PCT-US/JPW/A	8743

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EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 11/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/809,920	Taka-Aki Sato
Examiner	**Art Unit**
Mary Schmidt	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 16, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-7, 12-16, 21, 22, and 98-106* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-7, 12-16, 21, 22, and 98-106* is/are rejected.

7) ☒ Claim(s) *16* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on _____ is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 8
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Specification

1. Applicant is reminded of the proper language and format for an abstract of the disclosure

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

2. The abstract of the disclosure is objected to because it is longer than 150 words. Correction is required. See MPEP § 608.01(b).

3. On page 9 of the specification, under the brief description of the figures for Figure 5, the specification needs to be amended to reflect that figure 5, is actually two figures, figure 5A and figure 5B.

Drawings

4. The drawings have been reviewed by an official draftsman and have been approved.

Claim Objections

5. Claim16 is objected to because of the following informalities: the claim recites a genetic alteration set forth in Table 3. This recitation does not properly provide the claimed genetic alterations. Applicant is requested to specifically claim the genetic alterations, instead of referring to the table. Appropriate correction is required.

Restriction/Election

6. Applicant's election with traverse of Group II in Paper No. 11B, filed August 16, 2002, is acknowledged.

The traversal is first on the grounds that Groups I-IV "are not independent." Applicant states that "[u]nder M.P.E.P. 802.01, "independent" means "there is no disclosed relationship between the ... subjects disclosed, that is, they are unconnected in design, operation, or effect... ." The claims of Groups I-IV are related in that they are drawn to nucleic acid encoding TREX, TREX proteins, methods of screening for [in] TREX, and methods for diagnosing cancer which comprises detecting genetic alterations in the nucleic acid encoding TREX. In particular, Groups I and II are both directed to nucleic acid encoding TREX, and Groups III and IV are both directed to TREX proteins.

This is not found persuasive because MPEP 803.04 states that "[n]ucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121." The sequence of instant SEQ ID NO:3 in elected Group II is thus considered independent and distinct from the nucleic acid sequences of non-elected Group I.

The traversal is further on the grounds that "the Examiner must examine the application on the merits, even though it includes claims to distinct inventions, if the search and examination of an application can be made without serious burden. There are two criteria for a proper requirement for restriction, namely (1) the inventions must be independent and distinct; AND (2) there must be a serious burden on the Examiner if restriction is not required. Applicant maintains that there would not be a serious burden on the Examiner if restriction were not required. A search of prior art with regard to any of Groups I-IV would necessarily identify art for another Group. Since there is no serious burden on the Examiner to examine Groups I-VI in the subject application, the Examiner must examine the entire application on the merits."

This is not found persuasive since a search of Group II, the nucleic acid sequence of instant SEQ ID NO:3, would not require a search of instant SEQ ID NO:1, as in Group I. Furthermore, claims 38-39 have been canceled, therefore, Groups III and IV are not a consideration. Therefore, the search burden is distinct between Groups I and II, and restriction of two distinct nucleic acids is permissible under MPEP 803.04.

The requirement is still deemed proper and is therefore made FINAL.

The claims are further examined on the merits for the elected group drawn to human TREX sequences, such as instant SEQ ID NO:3.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 101-106 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for vectors and host cells in cell culture, does not reasonably provide enablement for vectors and host cells in a whole organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 101-106 are drawn to vector compositions "adapted for expression in a host cell" and host cells comprising vectors, wherein the host cells are eukaryotic, bacterial, insect or yeast cell, or mammalian cells. MPEP 2164.01 c) states that "[w]hen a compounds or compositions claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation." In the instant case, the new vector claims and host cell claims embrace host cells in a

whole organism mammal, including human. The claims thus read on gene therapy of a human by administration of vectors comprising the TREX nucleic acid for recombinant expression *in vivo*.

There is a high level of unpredictability in the prior art for the design and administration of gene therapy vectors to cells in a whole organism. Miller et al. taught that "[s]uccessful gene therapy requires not only the identification of an appropriate therapeutic gene for treatment of the disease, but also a delivery system by which that gene can be delivered to the desired cell type both efficiently and accurately." (Abstract) Note Anderson who taught on page 25, col. 2, lines 6-10, that "[t]he problems that investigators face in developing retroviral vectors that are effective in treating disease are of four main types: obtaining efficient delivery, transducing non-dividing cells, sustaining long-term gene expression...." These factors are considered unpredictable in the art and both of these articles further detail such problems in making and using vectors for successful expression of a desired protein (such as the instant TREX protein) in cells in a whole organism.

The instant specification as filed provides no teaching of the expression of instant SEQ ID NO:3, for instance, from a vector and administration into cells in a whole organism. Without further guidance, in view of the unpredictability in the art for successful design and use of any desired gene for gene therapy expression purposes, one of skill in the art would necessarily practice"trial and error" experimentation, the amount of which is considered undue, to make and use the instantly claimed nucleic acid sequences in a vector for use in a cell in a whole organism.

9. Claims 1-7, 12-16, 21-22 and 98-106 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to an isolated nucleic acid molecule encoding a Tumor necrosis factor Receptor-Associated Factor (TRAF) protein-interacting hereditary multiple extoses (TREX) protein. Claims 2-5 state that the nucleic acid molecule is a DNA, cDNA, genomic or RNA molecule. Claim 6 states that the isolated nucleic acid molecule of claim 1 is mammalian. Claim 7 states that the nucleic acid molecule of claim 1 is human. Claim 12 states that the nucleic acid molecule of claim 6 encodes the amino acid sequence of SEQ ID NO:4. Claim 13 states that the isolated nucleic acid molecule of claim 12 comprises an isoleucine zipper motif and a hereditary multiple extoses C (EXT C) domain. Claim 14 states that the nucleic acid molecule of claim 6 encodes a protein having substantially the same amino acid sequence as that in instant SEQ ID NO:4. Claim 15 states that the nucleic acid molecule of claim 6 encodes a protein which has the amino acid sequence as set forth in instant SEQ ID NO:4. Claim 16 is drawn to an isolated nucleic acid molecule encoding a mutant homolog of the mammalian Rumor necrosis factor Receptor-Associated Factor (TRAF) protein-interacting hereditary multiple extoses (TREX) protein whose genetic alteration is set forth in Table 3. Claim 21 states that the nucleic acid molecule of claim 6 comprises a human nucleic acid sequence set forth in SEQ ID NO:3. Claim 22 is drawn to a vector comprising the sequence of claim 1. Claim 98 is drawn to the isolated

nucleic acid molecule of claim 12, which is a deletion mutant. Claim 99 is drawn to the deletion mutant of claim 98, wherein the encoded mutant homolog comprises a tumor suppressor locus. Claim 100 is drawn to the deletion mutant of claim 98, wherein the encoded mutant homolog does not comprise a tumor suppressor locus domain. Claims 101-104 are drawn to expression vectors comprising the Tumor necrosis factor Receptor-Associated Factor (TRAF) protein-interacting hereditary multiple extoses (TREX) expressing sequences. Claims 105-106 are drawn to host cells comprising the vector of claim 101.

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The specification as filed teaches the identification of instant SEQ ID NO:3 encoding the protein of instant SEQ ID NO:4. The specification teaches on page 40 that [c]oimmunoprecipitation experiments indicated that not only TRAF3 but TRAF2 strongly and TRAF5 weakly binds to TREX.... These results suggest that TREX and TRAF proteins are physically associated in mammalian cells." The specification further teaches the roles of EXT family member proteins on pages 41-42 of the specification. On page 51, the specification states that "[t]he fact that the TREX candidate gene showed significant similarity with EXT gene family and mapped within the region deleted in a variety of tumor types, strongly suggests that it is therefore a novel member of the EXT gene family as well as a potential candidate fro several tumor phenotypes." The specification then teaches use of the primers in Table 2 (page 52) for the results obtained on pages 53 and 54. The results were that one patent with thyroid cancer, had a 9-base (3 amino acid) insertion in the TREX DNA.

The closest prior art is cited below as Van Hul et al. and Saito et al. Both of these references taught isolation of the same nucleic acid sequence as instant SEQ ID NO:3 and the same protein sequence as instant SEQ ID NO:4, (in view of GenEmbl AB007042 (Saito et al.), Gen Embl AF001690 (Van Hul et al.), and SwissProt_40 AC 043909; O00225 referencing both Saito et al. And Van Hul et al. for the protein sequence). They did teach that this TREX protein is a member of the family of EXT proteins involved in tumor suppression. It has been found that when EXT proteins are mutated they are involved in the bone tumor disease multiple exostosis

syndrome (EXT). Thus the instant SEQ ID NO:3, the TREX protein, is considered to have patentable utility based on its membership in this family of tumor suppressor proteins.

The claims lack written description because the specification as filed did not teach that applicant was in possession of a representative number of species of the genus of any possible TREX protein encoding nucleic acid as broadly claimed, including any deletion thereof as claimed in new claims 98-100. Only the sequence of instant SEQ ID NO:3 was known in the prior art and taught in the specification as filed as a human "TRAF interacting TREX protein". Neither rat or mouse sequences (claim 7) nor any other TREX from other species were taught by sequence in the specification as filed. The teaching on page 53 of the specification of the one patient with thyroid cancer having a 9-bp insertion in the TREX DNA does not provide a representative number of species of any deletion mutant (new claims 98-100). In the absence of a more specific description of the design criteria (ie., specific sequences and deletion modifications) needed to visualize a representative number of species of any possible TREX encoding nucleic acid sequence, one of skill in the art would not have sufficient written description of the claimed compounds. As such, the specification as filed does not teach that applicant was in possession of a representative number of species of the claimed invention at the time of filing.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1-7, 12-15, 21-22, 101-106 are rejected under 35 U.S.C. 102(a) as being anticipated by GenEmbl AF001690, Van Hul et al., Genomics 47 (2), 230-237 (1998).

GenEmbl database AF001690 (available Feb. 20, 1998), is relied upon to show that the sequence of instant SEQ ID NO:3 (human mRNA and cDNA). The database sequence header references the authors (Van Hul et al.) Genomics article. The referenced Genomics article further taught the elucidation of the nucleic acid sequence, from YAC (yeast artificial chromosomes) containing the genomic DNA (page 232, col. 1), and Clontech subcloning vectors (page 231, col. 1) containing expressed sequences (they thus taught vectors and cells comprising said vectors). Their expressed gene corresponds to the sequence of the protein of instant SEQ ID NO:4 (designated EXTL-3; see also SwissProt database O43909;O00225 confirming that the protein sequence Van Hul et al. call EXTL-3 is the same as instant SEQ ID NO:4). Van Hul et al. show on page 234 and 235 the alignment of EXTL-3 with other known EXT member proteins. MPEP 2112.01 teaches that "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially

identical processes, a *prima facie* case of either anticipation or obviousness has been established." Therefore, the sequence taught by Van Hul et al. having the same sequence of instant SEQ ID NO:4 comprises the zipper motif and EXT C domain claimed in instant claim 13.

12. Claims 1-3, 5-7, 12, 14, 15, 21, 22, and 101-102 are rejected under 35 U.S.C. 102(a) as being anticipated by GenEmbl AB011091 (available April 10, 1998).

GenEmbl AB011091 is relied upon the teach the sequence of instant SEQ ID NO:3 (mRNA and cDNA), and its location in the plasmid vector pBluescript II SK plus (GenEmbl report). MPEP 2112.01 states that "[w]here the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." Therefore, the sequence taught by GenEmbl AB011091, having a 99.9% homology to the entire coding region of instant SEQ ID NO:3, must inherently teach the claimed nucleic acid molecule encoding a Tumor necrosis factor Receptor-Associated Factor (TRAF) protein-interacting heredity multiple extoses (TREX) protein.

13. Claims 16 and 98-100 are free of the prior art because the closest prior art, GenEmbl AF001690, Van Hul et al., Genomics 47 (2), 230-237 (1998), did not teach nor fairly suggest the TREX having a genetic alteration as set forth in instant Table 3 (claim 16) nor deletion mutants (claims 98-100). A sequence search of instant SEQ ID NO:3 also revealed that the mRNA/cDNa

sequence in GenEmbl AB007042, Saito et al., Biochem. Biophys. Res. Commun. 243 (1), 61-66, 1998, was not available until Feb. 13, 1999 and the mRNA/cDNA sequence was not published in the journal article.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

M. M. Schmidt
November 4, 2002